

Assessment of Neurophysiologic Changes and Disease Activity in Patients with Chronic Rheumatoid Arthritis

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Abstract

Objective: The involvement of the peripheral nervous system is not uncommon in rheumatoid arthritis (RA); the most common disorders are multiple mononeuritis, sensor motor neuropathy, and entrapment neuropathy. Several auto-antibodies are associated with the disease, but of the most important are the anti-cyclic citrullinated peptide (anti-CCP) antibodies. However, little is known, about the role of high sensitive C-reactive protein (Hs-CRP) in relation to disease activity in RA. The objectives were to look for the frequency of peripheral nerves involvement in chronic rheumatoid arthritis patients and to investigate the correlations between clinical, hematological, serological, and neurophysiologic findings.

Methods: This study involved 48 patients with rheumatoid arthritis and 30 apparently healthy subjects as controls. Neurophysiologic assessment was performed for each patient and control subjects and the ELISA method was used for the quantitative measurement of serum anti-CCP antibodies and Hs-CRP concentrations by using special kits.

Results: The mean duration of the disease was 6.76 ± 0.795 years, the mean DAS28 for RA patients was 5.22 ± 0.131 , and the mean HAQ score was 1.00 ± 0.06 . Thirty-three (68.8%) of 48 cases with RA exhibited an electrophysiological evidence of neuropathy(ies): 14 (29.2%) patients with carpal tunnel syndrome (CTS), 9 (18.8%) patients with polyneuropathy, while 5 (10.4%) patients showed mononeuritis multiplex. There were highly significant increases in the mean values of serum anti-CCP antibody concentration (22.61 ± 2.34 Vs 5.47 ± 0.42 U/ml, $P < 0.001$), serum Hs-CRP concentration (10.05 ± 0.64 Vs 2.81 ± 0.22 mg/l, $P < 0.001$), and ESR (41.85 ± 2.7 Vs 11.73 ± 1.3 mm/hr, $P < 0.001$) in the RA group compared to the control group.

In patients with RA, significant negative correlations were observed between anti-CCP antibody concentration and sural nerve velocity ($r = -0.233$, $P < 0.05$) while significant positive correlation was found between anti-CCP antibody concentration with sural latency ($r = 0.231$, $P < 0.05$). The serum Hs-CRP level significantly positively correlated with the Stanford disability index ($r = 0.324$, $P < 0.05$), number of tender joint ($r = 0.296$, $P < 0.05$), and ESR ($r = 0.436$, $p < 0.01$).

Conclusions: The commonest neurophysiologic abnormalities were carpal tunnel syndrome (CTS), followed by polyneuropathy. Serum anti-CCP antibodies concentration, serum Hs-CRP concentration, and disability index (DI) are significantly correlated with neuropathy and occurrence of neuropathy depends on the activity and/ or severity of rheumatoid arthritis.

Keywords: rheumatoid arthritis, neuropathy, anti-CCP antibody, Hs-CRP.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and the destruction of synovial joints, leading to severe disability and premature mortality.^{1,2} It is estimated that 1% of the population suffers from this disease.^{3,4} Apart from involving the synovium in diarthroidal joints, RA can also involve virtually any system in the body, ranging from the lungs to the brain.^{5,6} These extra-articular features representing the systemic nature of the disease are seen in 10-41% of patients with RA.⁷

In rheumatoid arthritis (RA), neuromuscular complications such as neuropathy and myopathy are common.⁸ The neurological manifestations in RA include entrapment neuropathy, distal axonal polyneuropathy, and mononeuritis multiplex, as well as fulminant sensorimotor polyneuropathy, cervical myelopathy, and cerebral vasculitis.⁹

Although the precise etiology of RA remains unknown, there is strong evidence for autoimmunity, since several autoantibodies are associated with the disease. Beside the rheumatoid factor (RF), another group of autoantibodies has been detected in the serum of patients with RA: the anti-cyclic citrullinated peptide antibodies.¹⁰ Anti-CCP antibodies are antibodies against cyclic citrullinated peptides which are formed when arginine residues are deiminated by peptidylarginine deiminase (PAD) and emerged as clinically relevant diagnostic markers due to their high specificity for RA.¹¹⁻¹³

C-reactive protein (CRP) is the most

commonly used acute phase reactants (APRs) in RA to assess disease activity and progression.¹⁴ CRP is an acute phase reactant for trauma and infections and is mainly produced in the liver in response to systemic inflammations, resulting in increased blood CRP levels.^{15,16}

To our knowledge, an extensive and detailed electron neurophysiological study in RA patients is rare in the locality. Besides, the data concerning the correlations between nerve conduction, serological, and clinical parameters are scarce.

The current study aims to assess the pattern of neurological manifestations in patients with rheumatoid arthritis based on electrophysiological studies and to investigate the correlations between clinical, hematological, serological, and neurophysiologic findings.

METHODS

The subjects included in this study were divided into two groups: 1) 48 patients with RA who met the criteria of the American College of Rheumatology (ACR) for rheumatoid arthritis,¹⁷ comprising of 3 males and 45 females whose ages ranged from 23 to 60 years (mean \pm SE 44.15 \pm 1.32 years) and were recruited at the outpatient's clinic at Rheumatic Diseases and Medical Rehabilitation Centre in Duhok City, and 2) 30 apparently healthy subjects including 3 males and 25 females whose ages ranged from 30 to 50 years (mean \pm SE 41.12 \pm 0.94 years) which served as a control group. All patients and controls gave their informed consent and the study was approved by the local research ethics committee of the Faculty of Medical Sciences in Duhok.

All the patients with rheumatoid arthritis underwent complete clinical and rheumatologic examination. The activity of the disease was assessed by using the disease activity score DAS28.¹⁸ Functional disability was assessed by using the modified Stanford Health Assessment Questionnaire (MHAQ).¹⁹ The criteria for exclusion were a history of alcohol consumption, diabetes mellitus, family history of peripheral nervous system disorders, pregnancy, and thyroid gland disorders.²⁰

All the patients with RA and control subjects underwent nerve conduction studies for median (motor and sensory), ulnar (motor and sensory), peroneal (motor), tibial (motor), and sural nerves using a NIHON KOHDEN EMG/EP measuring machine (neuropack V07.01 version software) at a suitable room temperature (22-25°C). Bilateral nerve conduction studies were performed for the patients to improve the sensitivity of detecting possible neuropathy and the standard techniques for measurement of NCS parameters were used.²¹ Needle Electromyography (EMG) was also done for 20 randomly selected cases with RA. The

electro diagnostic protocol recommended by the American Diabetes Association was used.²² Quantitative serum anti-CCP antibody (ACCP) and serum high sensitivity C-reactive protein (Hs-CRP) assays were done using ELISA-type kits (manufactured by AESKU DIAGNOSTICS and Biocheck, respectively).

Statistical analyses were computer assisted using SPSS version 18. Variables were conveniently described by mean and SE (standard error). Unpaired -T tests were used to further explore the significance of difference in mean between the studied groups. For the strength of linear correlation between 2 quantitative variables, Spearman's rank linear correlation coefficient was used, and P value of <0.05 was regarded as statistically significant.

RESULTS

The mean age of patients with RA and control subjects were 44.15±1.32 and 41.12±0.939 years, P = 0.065, respectively. The mean duration of disease was 6.76±0.795 years, the mean disease activity score for RA was 5.22±0.131, and the mean HAQ score for functional disability was 1.00±0.06 (table 1).

Table (1): Clinical parameters among patients with rheumatoid arthritis

| <i>parameters</i> | <i>Rheumatoid arthritis Mean ±SE (No=48)</i> | <i>Control Mean ±SE(n=30)</i> |
|--------------------------------------|--|-----------------------------------|
| <i>Age(year)</i> | 44.15±1.32 | 41.12±0.94 |
| <i>Duration of Disease (year)</i> | 6.76 ±0.79 | - |
| <i>Disease activity score(DAS28)</i> | 5.22 ± 0.13 | - |
| <i>Stanford disability index(DI)</i> | 1.00±0.06 | - |

Four (8.3%) patients had low disease activity (DAS28 <3.2), twenty eight (58.4%) patients had moderate disease activity

(3.1<DAS28<5.1), and sixteen (33.3%) patients with severe disease activity (DAS28 >5.1) (table 2). HAQ disability index results

showed that 22 (45%) patients had mild disability (1 DI), 25 (52.1%) patients with moderate disability (2 DI), and 1 patient (2.1%) with severe disability (3DI) (table 3).

Table (2): Classification of disease activity score in rheumatoid arthritis patients (n= 48)

| <i>DAS28 Score</i> | <i>No. of patients</i> | <i>%</i> |
|----------------------------|------------------------|-------------|
| <i><3.2</i> | <i>4</i> | <i>8.3</i> |
| <i>3.2<DAS28<5.1</i> | <i>28</i> | <i>58.4</i> |
| <i>>5.1</i> | <i>16</i> | <i>33.3</i> |

DAS: Disease activity score

Table (3): Classification of functional disability by Stanford disability index in patients with RA (n = 48)

| <i>Stanford disability index(DI)</i> | <i>No. of patients</i> | <i>%</i> |
|--------------------------------------|------------------------|-------------|
| <i>Mild disability</i> | <i>22</i> | <i>45.8</i> |
| <i>Moderate disability</i> | <i>25</i> | <i>52.1</i> |
| <i>Severe disability</i> | <i>1</i> | <i>2.1</i> |

Table (4): Nerve conduction study findings in patients with rheumatoid arthritis (n= 48)

| <i>Categories</i> | <i>No.</i> | <i>%</i> |
|---|------------|-------------|
| <i>Normal</i> | <i>15</i> | <i>31.2</i> |
| <i>Carpal Tunnel Syndrome</i> | <i>14</i> | <i>29.2</i> |
| <i>Polyneuropathy (axonal and demyelination, sensori-motor)</i> | <i>8</i> | <i>16.7</i> |
| <i>Mononeuritis multiplex</i> | <i>5</i> | <i>10.4</i> |
| <i>Tibial neuritis</i> | <i>4</i> | <i>8.3</i> |
| <i>Polyneuropathy (axonal)</i> | <i>1</i> | <i>2.1</i> |
| <i>Peroneal neuritis</i> | <i>1</i> | <i>2.1</i> |

Fifteen patients (31.3%) showed normal nerve conduction, fourteen patients (29.2%) were found to have carpal tunnel syndrome (CTS), eight patients (16.7%) had polyneuropathy of mixed type (axonal and demyelinating pattern), one patient (2.1%) with polyneuropathy of

axonal type, five patients (10.4%) with mononeuritis multiplex, four patients (8.3%) with tibial neuritis, and one patient (2.15%) with peroneal neuritis (peroneal entrapment) (table 4). Needle EMG findings in 20 patients with RA showed ten (50%) patients had

normal EMG parameters: normal insertional activity, no spontaneous activity, and normal motor unit action potential (MUAP) parameters (Normal duration (5-15 ms), amplitude (100µv-2mv), and number of phases of MUAP (2-4 phases)). However, 10 (50%) of the patients showed reduced recruitment and interference pattern with the normal MUAP

parameters (table 5).

The mean values of serum anti-CCP antibody concentration, serum Hs-CRP concentration, and erythrocyte sedimentation rate (ESR) were highly significantly increased (P<0.001) in the RA group compared to the apparently healthy controls (table 6).

Table (5): Categories of EMG findings in patients with rheumatoid arthritis

| | <i>EMG parameters</i> | <i>EMG findings</i> | <i>No (N=20)</i> | <i>%</i> |
|--------------------------------------|---|---------------------|----------------------|------------|
| <i>Normal EMG findings</i> | <i>Insertional activity</i> | <i>Normal</i> | 10 | 50 |
| | <i>Spontaneous activity</i> | <i>No</i> | | |
| | <i>Recruitment and interference pattern</i> | <i>Normal</i> | | |
| | <i>Duration(5-15ms),amplitude(100µv-2mv) and phases of voluntary motor unit potential(2-4 phases)</i> | <i>Normal</i> | | |
| <i>Abnormal EMG findings</i> | <i>Insertional activity</i> | <i>Normal</i> | 10 | 50 |
| | <i>Spontaneous activity</i> | <i>No</i> | | |
| | <i>Recruitment and interference pattern</i> | <i>Reduced</i> | | |
| | <i>Duration(5-15ms),amplitude(100µv-2mv) and phases of voluntary motor unit potential(2-4 phases)</i> | <i>Normal</i> | | |
| <i>Total</i> | | | <i>20</i> | <i>100</i> |

Table (6): Level of serum anti-CCP antibody, serum Hs-CRP concentrations, and ESR in the rheumatoid arthritis patients and controls

| Parameters | Healthy control Mean ±SE (n =30) | Rheumatoid arthritis Mean ±SE (n =48) | p-Value |
|--------------------------------|--|---|---------|
| Serum anti-CCP antibody (U/ml) | 5.47±0.42 | 22.61±2.34 | < 0.001 |
| Serum Hs-CRP (mg/l) | 2.81±0.22 | 10.05±0.64 | < 0.001 |
| ESR(mm/1 st hr) | 11.73±1.3 | 41.85±2.7 | < 0.001 |

The DAS28 score was significantly negatively correlated with hemoglobin concentration ($r = -0.304$, $P < 0.05$), but significantly positively correlated with Hs-CRP concentration ($r=0.320$, $P < 0.05$, figure1) and ESR ($r=0.614$,

$P < 0.001$). Interestingly, the serum Hs-CRP level was significantly positively correlated with the Stanford disability index ($r=0.324$, $P < 0.05$), number of tender joint ($r=0.296$, $P < 0.05$) and ESR ($r=0.436$, $p < 0.01$).

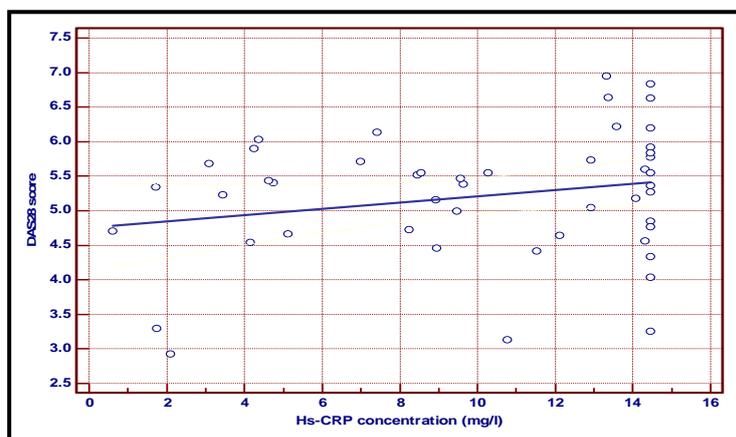


Figure (1): Scatter diagram with fitted regression line showing the correlation between DAS28 score and serum Hs-CRP concentration (mg/l) among RA patients ($r=0.320$, $p=0.001$)

Significant inverse correlations were observed between age with ulnar motor velocity ($r = -0.504$, $P < 0.01$), sural sensory velocity ($r=-0.442$, $P < 0.001$), median sensory velocity ($r=-0.313$, $P < 0.01$), and ulnar sensory velocity ($r=-0.299$, $P < 0.05$) and positive correlation with median nerve sensory latency ($r=0.369$, $P < 0.001$).

In addition to that, serum anti-CCP antibody

concentration positively correlated with serum Hs-CRP concentration and ESR; however, it negatively correlated with hemoglobin concentration ($r=0.623$, $r=0.243$, and $r=-0.246$, $P < 0.01$, $P < 0.01$ and $P < 0.05$, respectively) (figures 2). Anti-CCP antibody concentration was significantly negatively correlated with sural nerve velocity ($r=-0.233$, $P < 0.05$) (figure 3), and positively correlated with sural latency ($r=0.231$, $P < 0.05$). Hs-CRP was negatively

correlated with peroneal (extensor digitorum brevis compound muscle action potential (CMAP)) amplitude ($r = -0.329$, $P < 0.05$) and peroneal motor velocity ($r = -0.322$, $P < 0.05$).

In addition, there was a significant positive correlation between median sensory latency and the Stanford disability index ($r=0.285$, $P<0.05$).

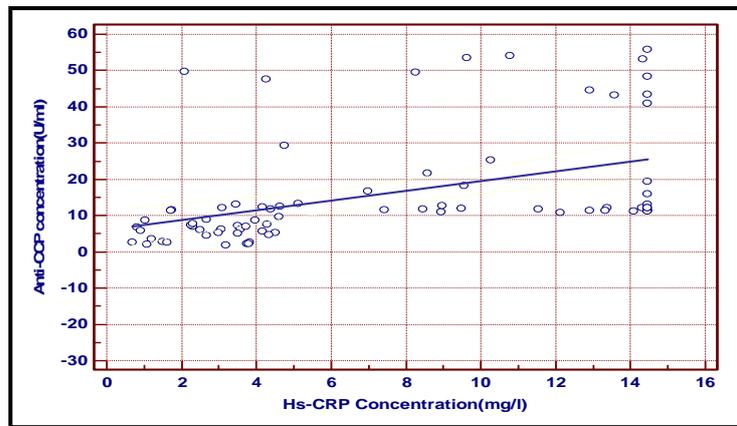


Figure (2): Scatter diagram with fitted regression line showing the correlation between serum anti-CCP antibody concentration (U/ml) and serum Hs-CRP concentration (mg/l) among RA patients ($r=0.623$, $p =0.001$)

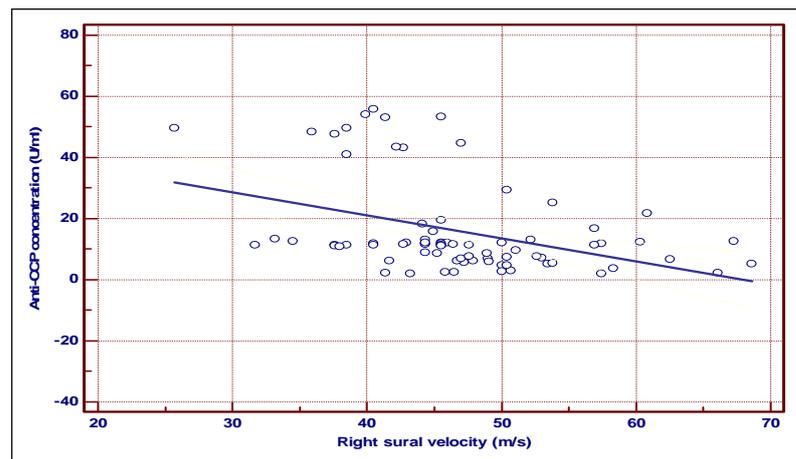


Figure (3): Scatter diagram with fitted regression line showing the correlation between serum anti-CCP antibody concentration and sural velocity among RA patients ($r =-0.466$, $p=0.001$).

DISCUSSION

Patients with rheumatoid arthritis may have different types of peripheral neuropathy like entrapment neuropathy, distal axonal predominantly sensory neuropathy, and multiple mononeuropathy (mononeuritis

multiplex), as well as fulminant sensori-motor polyneuropathy.²³It is often difficult to diagnose slight or early neuropathies with any certainty, and the study of the peripheral neuromuscular system is made difficult by symptoms resulting from pain and stiffness of peripheral joints.²⁴However, it is possible by

means of electrophysiological examination to show the presence and distribution of even subclinical neuropathies. Therefore, the assessment of peripheral nerve function is important in detecting extra-articular disease manifestations.

In this study, we found electrophysiological evidence of neuropathy in 33 (68.8%) of 48 cases with RA, which was higher than other reports,^{5,9,24,25} and in consistent with other studies.^{23,26} CTS was the commonest type of neuropathy in patients with RA (29.2%), followed by polyneuropathy (18.8%) and mononeuritis multiplex (10.4%). Similar results were noticed in other studies.^{19,27} The different patterns of peripheral nerve damage and, in particular, the occurrence of demyelination suggest that pathogenic mechanisms other than vasculitis may participate in the pathogenesis of neuropathy in RA patients.

Apart from decreased recruitment and interference pattern in 50% of the patients with RA, no other abnormality such as spontaneous discharge or abnormal motor unit potential were observed. These findings are consistent with the results observed by Fahrer *et al.*²⁸ Decreased recruitment and interference pattern are most likely due to muscle weakness and pain leading to the inhibition of grip strength directly and indirectly by arthrogenous muscle inhibition as a result of afferent impulses from inflamed joint mechanoreceptors and joint nociceptors.²⁹

In the present study, none of the healthy control subjects had a positive anti-CCP antibodies value and the mean serum anti-CCP antibodies level was significantly higher in the RA patients compared to the healthy control

subjects (22.61 ± 2.34 and 5.47 ± 0.42 U/ml, $P=0.001$).

Patients with rheumatoid arthritis showed increased serum levels of anti-CCP antibodies and Hs-CRP in comparison to healthy controls. Although limited data are available concerning the level of Hs-CRP in rheumatoid arthritis, our findings are consistent with other studies,^{30,31} and indicate that serum Hs-CRP levels are associated with disease activity in patients with rheumatoid arthritis.

Results in the present work showed significant negative correlations of age with sensory conduction velocities of sural, median and ulnar nerves and positive correlation with median nerve sensory latency. This indicates that the age of the patient acts as an important factor for determining the susceptibility of the patient to develop neuropathy (particularly sensory neuropathy).

Moreover, there were significant negative correlations between the Stanford disability indexes with the motor velocity of the ulnar nerve, anti-CCP antibodies concentration with the sural nerve velocity, Hs-CRP concentration with the amplitude and the motor velocity of the peroneal nerve.

Our findings indicate that CTS and polyneuropathy are the commonest types of neuropathies in patients with RA, and the presence of a significant correlation of serum anti-CCP antibodies, Hs-CRP concentrations, and the disability index (DI) with neuropathy in RA patients pointed to the occurrence of neuropathy in RA which depends on the activity and/or severity of rheumatoid arthritis.

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تقييم التغيرات الفسيولوجية العصبية ونشاط المرض لدى المرضى المصابين بالتهاب المفاصل الرثوي المزمن

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الملخص

خلفية الموضوع والأهداف: الإصابات السريرية للجهاز العصبي المحيطي شائعة في التهاب المفاصل الرثوي ومن بينها التهاب الأعصاب المحيطية، والاعتلال العصبي الحسي والحركي، واعتلال عصبي أنحصاري. هنالك الكثير من الأجسام المضادة التي لها ارتباط بهذا المرض، ولكن من أهمها (Anti-CCP anti-bodies). المعلومات المتوفرة حول دور تركيز (Hs-CRP) في تقييم نشاط المرض في التهاب المفاصل الرثوي قليلة. الأهداف من هذه الدراسة هي البحث عن نسبة تدخلات (التهاب) الأعصاب المحيطية في مرضى التهاب المفاصل الرثوي المزمن والبحث عن احتمالية وجود علاقة بين النتائج السريرية والمصلية والميماتولوجية والفسيولوجية العصبية.

المواد وطريقة العمل: شملت هذه الدراسة 48 مريضاً يعانون من التهاب المفاصل الرثوي و30 شخصاً أصحاء كمجموعة ضابطة. تم إجراء فحص تخطيط العصب لدراسة التغيرات الفسيولوجية العصبية عند المرضى ومقارنتها بالأصحاء. وتم استخدام طريقة ELISA لقياس (Anti-CCP antibodies) و (Hs-CRP concentration) في المصل.

النتائج: كان متوسط مدة مرض التهاب المفاصل الرثوي (0.795 ± 6.76 سنة)، درجة نشاط المرض (5.22 ± 0.131)، والعجز الوظيفي (HAQ disability index) (0.06 ± 1.00).

تبين ان ثلاثة وثلاثين مريضاً (68.8%) من أصل 48 لديهم اعتلال عصبي: 14 منهم (29.2%) كانوا مصابين بمتلازمة النفق الرسغي (CTS)، 9 (18.8%) يعانون من اعتلال الأعصاب (polyneuropathy)، بينما 5 (10.4%) يعانون من التهاب الأعصاب المتعددة (mononeuritis multiplex). من نتائج الفحوصات المخبرية وجدت زيادة معنوية في قيم تركيز (serum anti-CCP antibodies) (22.61 ± 5.47 مقابل 0.42 ± 5.47 U / مل، $P < 0.001$)، و (Hs - CRP concentration) (0.64 ± 10.05) مقابل 0.22 ± 2.81 ملغم / لتر، $P < 0.001$ ، وسرعة ترسب الكريات الحمراء (41.85 ± 2.7) مقابل 11.73 ± 1.3 مم / ساعة، $P < 0.001$ لدى المرضى بالمقارنة مع الأشخاص الأصحاء.

وجد ارتباط سلبي ومعنوي لدى مرضى التهاب المفاصل الرثوي بين تركيز (Serum anti-CCP Antibodies) وسرعة توصيل العصب الربلي ($r = -0.233$ ، $P < 0.05$) وارتباط إيجابي بين (serum anti-CCP antibodies) مع زمن الكمون للعصب الربلي ($r = 0.231$ ، $P < 0.05$).

تبين ان تركيز (serum Hs-CRP concentration) له ارتباط إيجابي مع العجز الوظيفي ($r = 0.324$ ، $P < 0.05$)، وعدد المفاصل المتألمة ($r = 0.296$ ، $P < 0.05$) وسرعة ترسب الكريات الحمراء ($r = 0.436$ ، $P < 0.01$).

الاستنتاجات: الاصابات الفسيولوجية العصبية الأكثر شيوعاً هي: متلازمة النفق الرسغي (CTS)، تليها التهاب الأعصاب المحيطية (polyneuropathy). تركيز (Hs - CRP (anti-CCP Antibodies) في المصل والعجز الوظيفي يرتبطان معاً لاعتلال العصبي. وحصول الاعتلال العصبي يعتمد على فعالية او / ونشاط مرض التهاب المفاصل الرثوي.

الكلمات الدالة: التهاب المفاصل الرثوي المزمن؛ التغيرات الفسيولوجية العصبية، نشاط المرض.